

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 03D–0007]

Draft Guidance for Industry on Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms—Recommendations for Clinical Evaluation; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled “Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms—Recommendations for Clinical Evaluation.” The agency is revising its guidance for industry entitled “Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women,” which was issued in March 1995 (the 1995 guidance). Once finalized, this guidance will replace the 1995 guidance.

DATES: Submit written or electronic comments on the draft guidance by [*insert date 60 days after date of publication in the **Federal Register***]. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information (HFD–240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send on self-addressed adhesive label to assist that office in processing

your requests. Submit written comments on the draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Margaret Kober, Center for Drug Evaluation and Research (HFD-580), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4243.

SUPPLEMENTARY INFORMATION:

I. Background

In March 1995, the agency issued a guidance entitled “Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women”. The agency was revising the 1995 guidance when the results of a substudy of the National Institutes of Health (NIH) Women’s Health Initiative (WHI) trial were made available to the public.¹ In light of the interim results of the WHI substudy, on September 10, 2002 (67 FR 57432), the agency withdrew the 1995 guidance. Once finalized, this guidance will replace the 1995 guidance.

In the WHI substudy, postmenopausal women who took conjugated estrogen 0.625 milligram (mg) combined with medroxyprogesterone acetate 2.5 mg had higher risks of several serious adverse events relative to those women who took placebo. Conjugated estrogens alone also increased the rates of cardiovascular disease compared to placebo. Other doses of conjugated

¹ The results of the NIH Women’s Health Initiative trial were reported in the *Journal of the American Medical Association*, 288: 321-333, 2002.

estrogens and medroxyprogesterone acetate and other combinations of estrogens and progestins were not studied in the WHI. However, in the absence of comparable data, the risks of serious adverse events should be assumed to be similar because other studies show that estrogens and progestins are associated with these types of events.

This draft guidance revises the 1995 guidance in several ways. For example, the draft guidance no longer uses the phrase “hormone replacement” because neither estrogen alone nor estrogen/progestin treatments for symptoms of menopause should be considered replacement hormones. The guidance only addresses two indications (moderate to severe vasomotor symptoms and moderate to severe vulvar and vaginal atrophy symptoms) and explains under what conditions both indications can be studied concurrently in a single trial. For other indications, such as the prevention of osteoporosis, sponsors are asked to direct inquiries to the appropriate review division in the Center for Drug Evaluation and Research. A section entitled Primary Endpoints has been added for each indication, and the Study Analysis section has been modified to clarify analyses of the primary endpoints. The Monitoring section for drug products containing estrogen plus progestin has been expanded. The additions to this section were made to address diagnostic ambiguities in the efficacy evaluation for protection of the endometrium.

This level 1 draft guidance is being issued consistent with FDA’s good guidance practices regulation (21 CFR 10.115). The draft guidance represents the agency’s current thinking on recommendations for clinical evaluation of estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.

An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit to the Dockets Management Branch (see **ADDRESSES**) written or electronic comments regarding the draft guidance. Submit a single copy of electronic comments to <http://www.fda.gov/dockets/ecomments> or two hard copies of any written comments, except that individuals may submit one hard copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

III. Electronic Access

Persons with access to the Internet may obtain the draft document at either <http://www.fda.gov/cder/guidance/index.htm> or <http://www.fda.gov/ohrms/dockets/default.htm>.

Dated: January 23, 2003.

Margaret M. Dotzel,

Assistant Commissioner for Policy.

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